REMARKS

Applicants have amended the claims to make explicit that which was implicit. Namely, that the chemokine binding site is one that binds to either chemokine receptor CCR5 or CXCR4. This is supported throughout the specification. See for example, page 6, lines 20 to 24. Claim 1 also makes explicit that which was taught in the specification, that there are four glycosylation sites proximal to the specified binding sites. Claims 4 and 6 specify the location of those sites in one strain so corresponding sites can be determined. This is supported throughout the specification. See particularly pages 19 and 20. The amendment to Claim 14 is editorial in nature. New claims 15 and 16 are supported at page 23. As such these amendments do not constitute new matter and their entry is respectfully submitted.

Claims 1-4, 6 and 14 were rejected under 35 U.S.C., §112, second paragraph.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Applicants respectfully submit that the objected to terms would be well known by those skilled in the art. The HIV virus and the gp120 protein are among the most extensively studied and characterized virus proteins. Indeed, the references that the Examiner has cited against the claims, which includes both patents and literature references, show that all the objected to terms are well known to the skilled artisan.

Turning specifically to the rejections, applicants have the following comments. Applicants are entitled to claim the modified gp120 broadly. It is well known how the protein varies. Indeed, the terms "conserved regions" mean that the amino acid residues are conserved

across the various strains whereas those regions referred to as "variable" have variability in amino acid residues among the strains. But one can readily determine the protein and the various regions within that protein.

The objected to phrase "at least" while relative is not indefinite because it means exactly what it says when read in context with the other words. For example, when used to refer to at least two conserved regions of the envelope protein, the skilled artisan would know that any number between two and all five of the conserved regions of the envelope gp120 protein can be present. With respect to where the phrase "at least" refers to the glycosylation sites proximal to the CD4 binding site or the chemokine receptor binding site, the phrase specifies that at least two of the four sites have been altered and includes the situations where three of the sites and all four of such sites are altered. Thus, the phrase precisely defines and tells the skilled artisan the choices that are possible.

With respect to the Examiner's objection to phrase "portion of at least two conserved regions", applicants again submit that the precise deletion in a particular portion does not need to be defined because applicants have specified that whatever the deletion is, the modified polypeptide must maintain the overall three dimensional structure of a discontinuous conserved epitope of the wild-type gp120. Thus, the claim functionally puts limits on what regions must be present, but does not require amino acid residues that are not important. This language has been accepted by the U.S. PTO in patents including those relied upon by the Examiner.

Turning to the statement about the CD4 binding site and chemokine binding site not being defined, applicants submit that the skilled artisan is aware of what is talked about, particularly in light of the specification. As the specification clearly discussed and is well known in the art, the chemokines that gp120 binds to are not unlimited, but rather with respect to gp120,

are essentially CCR5 and CXCR4 (See for example page 6). The skilled artisan would also know that amino acids in the gp120 C3 and C4 regions are implicated in CD4 binding (See for example page 4 of the specification). The present application goes on to teach the explicit CD4 binding site as well as the chemokine binding sites. The present application provides the three-dimensional structures of gp120. See Figures 1 through 5. In particular, if one looks at Figure 4A through 4D, one can see the spacial relationship of epitopes on the HIV-1 gp120. For example, Figure 4B shows residues of the CD4i binding site and CD4bs. See also Figure 4D. The application teaches that the vast majority of the gp120 residues involved in the formation of CD4i epitopes are located either within a specific antiparallel beta sheet or in nearby structures. The specification goes on to teach at page 45 how CD4bs epitopes are determined, and where they are located. See Table 1 and Figures 4B and 4C.

The application then goes on to teach that there are in fact four specific glycosylation sites that surround these sites. Thus, the skilled artisan can readily use the specification and to determine the exact changes in the site between the different clades.

Turning to the Examiner's objection of the phrase "discontinuous conserved epitope," the specification explicitly teaches that this is an eptitope conserved among the various strains and the specification shows how to determine specific epitopes. Additionally, the references cited show that such a phrase is clearly known to the skilled artisan.

With respect to the Examiner's objection to the use of the phrase "that the skilled artisan would not know what a 'hydrophobic amino acid residue is'" applicants respectfully submit that this is a well known term in the art and that the Examiner is treating the skilled artisan as if none of the work in these proteins that has dated back almost two decades exists.

Again, applicants respectfully submit that the Examiner's objection to the phrase "pan reactive T-Cell helper epitopes" similarly ignores the level of knowledge of the skilled artisan in this field.

With respect to the Examiner's objection to the phrase "at least" in the later claims, applicants incorporate by reference the specific discussion concerning this phase above.

Thus, applicants respectfully submit that all rejections of the claims under 35 U.S.C. §112, second paragraph should be withdrawn.

Claims 1-4, 6 and 14 were rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The Examiner has acknowledged that the specification is enabling for making some recombinant HIV gp120s, wherein the HIV gp120 can be modified at certain positions of the glycosylation site near the discontinuous epitope of CD4bs for deletion of the variable regions (V1, V2 and/or V3) which enables better exposure of the hidden CD4bs in the interface of the HIV gp120 molecules. However, the Examiner contends that it does not provide enablement for modifying alternately any or all glycosylation sites near the CD4bs and maintaining at least any or all portions of two conserved regions, wherein the molecule retains the three dimensional structure. However, with respect to making modifications of the gp120 protein wherein three dimensional structures are maintained, the application explicitly teaches how. Further, the Examiner has cited numerous references as prior art against the present invention, which show how one can delete various portions of the variable regions and even portions of conserved regions, while maintaining the overall three dimensional structure of a discontinuous epitope of the native gp120 protein. See for example U.S. Patent No. 5,817,316 and Olshevsky. The Examiner points to references to show how certain changes can dramatically affect gp120

binding to CD4. Yet those same references establish that applicants can readily determine the effect a particular amino acid change has on binding. Moreover, the Examiner ignores the further teaching of the present specification. Particularly the teaching with respect to the three dimensional structure of the protein, as exemplified in Figures 1 through 5, and the text discussing those figures, which explicitly show the interrelationship between different regions and how one can modify those regions. See particularly the discussion with respect to the epitopes and binding sites and the variability of residues at pages 41 through 50, and Table 1.

The skilled artisan has been taught by the present application, particularly in light of the prior art, how to maintain the overall three dimensional structure of gp120. For example, use of specific linker amino acid residues to maintain proper conformation, what regions to delete and how to remove glycosylation sites. E.g, by substituting different amino acid residues or deleting amino acid residues. Moreover, as taught in the present specification there are **four** glycosylation sites that surround both sites. Thus, while gp120 contains at least 24 glycosylation sites, 20 of those 24 are not relevant to the claims.

The skilled artisan would also know which four sites to use. For example, the specification explicitly teaches that those sites correspond to positions 197, 276, 301 and 386 of HIV-1 strain HXBc2. Given the over two decades of work studying and elucidating HIV and strain to strain variation, the skilled artisan readily knows the corresponding sites.

The Examiner's discussion of Ho is not on point because Ho did not maintain a three dimensional structure that corresponds to the wild-type protein. Rather, Ho taught that changing conformation can affect binding of conformationally dependent antibodies.

The Examiner's statement that some of the conserved regions contain amino acid residues that are indispensable for maintaining the CD4 binding site, with citation to Thali,

shows that the skilled artisan readily knows what portions of the conserved regions are required. In this art field the present specification is more than sufficient. Indeed, Table 1 shows conserved epitopes for neutralizing antibodies that have been identified on the gp120 core, the specific residues and their characteristics. The specification teaches the interrelationship of specific regions and specific epitopes. Claim 4 specifies what the particular epitope is and corresponding glycosylation sites.

Finally, with respect to the Examiner's statement that random alterations of glycosylation sites may affect the CB4 receptor binding site, that is irrelevant for the present application. The claims of the present application do not require that the modified gp120 has the functional properties of the wildtype gp120. Rather, applicants taught that this modified protein can be used, for example, to raise a greater range of antibodies to a conserved epitope and/or enhanced immunogenicity for broadly neutralizing epitopes. That does not require a biologically active protein.

Finally, turning to the Examiner's statement with respect to the issue of working examples, applicants respectfully submit that the techniques taught in the present specification, given the state of the art, do not raise any question that one can prepare a gp120 antibody that has the required characteristics. With respect to maintaining the three dimensional structure involving a discontinuous epitope such as CD4bs, the specification teaches how to do this. The cited Sodroski patent establishes that modified gp120s where variable and conserved regions are deleted while maintaining discontinuous conformation epitopes can be prepared. How to introduce a Pro residue is well known within the art as is how to increase hydrophobicity. The specification explicitly teaches where that interface is and how to increase such hydrophobicity. The specification further teaches how to introduce a pan reactive T-cell helper epitope within an

explicit citation to Alexander, et al. (see page 49) and that this can help overcome immunological tolerance to self proteins. With respect to where this epitope can be placed, applicants suggest that one site might be the immunologically silent region (See the paragraph bridging pages 48 and 49). Other sites can be readily used.

Accordingly, applicants respectfully submit that the claims comply with 35 U.S.C. §112, first paragraph and that this rejection should be withdrawn.

Claims 1-4 and 6 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application Serial No. 09/446,820.

Applicants note that this is a provisional rejection. Applicants wish to hold this rejection in abeyance until such time as the other rejections are withdrawn and will consider filing a terminal disclaimer to expedite prosecution.

Claims 1 – 4 and 6 were rejected under 35 U.S.C. § 102(e) as being anticipated by Sodroski et al. (U.S. Patent No. 5,817,316A).

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Applicants respectfully submit that the myriad of references that the Examiner has cited in no way teach or suggest the present invention. While references such as Sodroski, et al. teach modified gp120 polypeptides comprising conserved region which have variable regions deleted while maintaining the overall three dimensional structure of the gp120 protein, this and other references in no way teach or disclose removing the specific glycosylation sites specified here. Given the 24 glycosylation sites presently in gp120, the claims teaching use of these four sites is

in no way suggested or disclosed by any of the references either individually or if they were to be conbined together. This will be more specifically discussed below.

Turning to the Sodroski patent, it is directed to deletion of the variable loop regions of gp120. Although Sodroski does disclose that in certain modifications sugars can be removed, it does not disclose or suggest modification of the glycosylation sites taught here. The present invention is directed to the finding that specific sugar residues found on gp120 play a critical role in its structure, and can be modified to generate an improved immunogen.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(a) as being anticipated by Cao et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Cao does not teach or suggest the desirability of mutating the specific glycosylation sites taught by the applicants. Furthermore, the modified gp120 proteins of Cao do not contain modifications of the claimed sites.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ho et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The gp120 protein produced in Ho is either unglycosylated or HIV-1 gp120 from patients. When recombined, it is expressed in either a bacterial system, *E. coli*, or a yeast system. Because bacteria do not have the enzymes to add sugars to proteins, *any* protein produced in a bacterial system is necessarily not going to be glycosylated, and consequently cannot fold into its native conformation. Gp120 expressed in yeast systems also do not fold

correctly. To argue, as the Examiner does, that an unglycosylated, mis-folded protein such as that described by Ho anticipates the present invention is to ignore the limitation of the claims that requires that the modified polypeptide maintains its overall three-dimensional structure. Further, there is nothing in Ho that in any way teaches or suggests the particular glycosylation sites.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Wyatt et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Wyatt is not directed to sugar removal, and it does not teach removal of the specific glycosylation sites taught here. Applicants reiterate that the present invention teaches the important role specific sugar residues play in the structure of gp120, and how to modify those sites to create a better immunogen.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Binley et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Binley teaches another modified gp120 protein, in which variable loops V1, V2 and V3 are deleted, and seven of the twenty-four possible glycosylation sites are deleted. Again, Binley fails to provide any teaching regarding the desirability of modifying the four critical glycosylation sites of the present invention. In fact, the sugars have been indiscriminately removed, and the gp120 produced there is not expected to function as an immunogen, given how large the deletions are.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Arthos et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Arthos discloses a gp120 protein expressed in *E. coli*. As described above, glycoproteins produced in bacterial systems are not glycosylated, and the gp120 of Arthos is mis-folded. Thus, Arthos does not disclose a gp120 variant that maintains its three dimensional structure, as required by the claims.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 14 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bolmstedt, 1996.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The gp160 protein of Bolmstedt has three sugars removed, at residues 406, 448, and 463. However, these are not the sugars removed in the present invention. Furthermore, these sugars were not targeted for modification based upon knowledge of the three-dimensional structure of gp120, nor would they in any way suggest the present deletions.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lee et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Lee discloses individual variants of gp120 in which only one of the twenty-four glycosylation sites has been modified, so that no sugar residue is added at that position.

However, the present invention requires that at least two of the four specified sugars are deleted; thus, the modification of any one of these four sites does not anticipate the present invention. While Lee does disclose certain combinations of deletions, it does not disclose or in any way suggest the combinations of the particular sites taught here. Furthermore, the specific glycosylation sites deleted here are based upon structural considerations, and are designed to improve immunogenicity of the gp120 variant. In contrast, Lee provides no structural or rational basis for the modifications made.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 14 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bolmstedt, 1991.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

While the gp120 protein of Bolmstedt removes two sugars, at residues 390 and 447, these are not the sugars removed in the present invention. There is no suggestion of the present invention.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Essex.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The gp120 variants disclosed by Essex are apparently designed to remove as many sugars as possible. For example, claim 1 of Essex is directed to a mutant HIV envelope protein in which "said mutant glycoprotein being sufficiently deglycosylated such that the total molecular mass ... is less than 90% [of wildtype]." More particularly, Essex teaches removal of many

sugars, in combinations which do not make sense in terms of immunogenicity. Furthermore, while Essex does disclose deglycosylating gp120 at residue 386, it does not teach or suggest any modifications at the other three sites required by applicants, namely those corresponding to residues 197, 276, and 301.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Earl.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Earl merely teaches a series of gp120 proteins which are truncated. While certain truncations will remove certain glycosylation sites, nothing in Earl teaches the use of site-directed modification of the sugars proximal to the CD4 or chemokine binding sites to design an improved immunogen.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Wu.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Wu teaches that variable loop deleted gp120 proteins can be expressed in a *Drosophila* cell line. However, Wu in no way teaches the modification of the four specified sugar residues taught by the present invention, nor does it provide any teaching regarding the desirability of making such mutations to improve immunogenicity.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Haigwood.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The gp120 proteins produced in Haigwood are expressed in yeast, without normal glycosylation, with some variable regions deleted. These variants are all either peptides or mis-folded proteins. Furthermore, every gp120 protein expressed in yeast so far has been mis-folded. Indeed, Haigwood even describes these polypeptides as "denatured" in the abstract.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Pollard.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Pollard merely reports another gp120 variable loop deletion, in which there is no teaching regarding specific removal of particular glycosylation sites.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 1 – 4 and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lekutis et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The sites which are mutated in the gp120 of Lekutis are not near the position of the discontinuous CD4 binding site, as contended by the Examiner, but rather are cystines, involved in disulfide bond formation. Thus, it is clear that none of these specific residues could be the glycosylation sites of the present invention.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

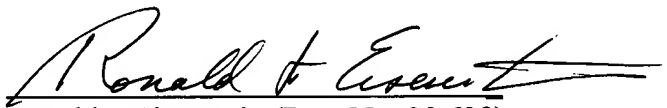
Accordingly, in view of the foregoing, applicants respectfully submit that all claims comply with 35 U.S.C. § 102 and 103.

In view of the foregoing, it is respectfully submitted that all claims are in condition for allowance. Early and favorable action is requested.

If any additional fee is required, charge Deposit Account No. 50-0850.

Date: April 18, 2003

Respectfully submitted,



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